ASYMMETRIC IMINE HYDROGENATION PROCESSES

FIELD OF THE INVENTION

The present invention relates to the field of catalytic hydrogenations, particularly catalytic asymmetric hydrogenation processes of the reduction of imines to amines in which the catalytic system includes a ruthenium complex containing (1) a diamine and (2) a diphosphine or two monodentate phosphines ligands.

BACKGROUND OF THE INVENTION

There is continuously a growing demand for enantiomerically pure amines in the pharmaceutical, agrochemical and fine chemicals industries. Over the past decade, there has been significant efforts directed towards developing procedures for asymmetric imine hydrogenations. Although many highly enantioselective chiral catalysts and catalytic processes are available for the asymmetric hydrogenation and transfer hydrogenation of C=C and C=O bonds, there are only a few widely applicable and feasible processes for effective reduction of the analogous C=N function of imines. The production of chiral amines via this methodology still represents a major challenge.

In 1997, B.R. James reviewed the preparation of chiral amines by homogeneous catalytic hydrogenation reactions involving metal complexes (James, *Catalysis Today* **1997**, 37, 209-221). The review by James names several systems based on rhodium for the asymmetric hydrogenation of imines but they suffer from drawbacks, such as low enantioselectivity or severe reaction conditions. In United States Patent No. 6,037,500, X. Zhang et al. disclosed the use of BICP, a chiral diphosphine ligand, on rhodium and iridium in the asymmetric hydrogenation of internal C=N bonds at 1000 psi H_2 at room temperature to produce amines with e.e. ranging from 65 to 94%. Spindler and co-workers demonstrated the use of *in situ* generated iridium JOSIPHOS complexes for the enantioselective hydrogenation of imines (Spindler et al., *Angew. Chem., Int. Ed. Engl.*, **1990**, 29, 558; Blaser and Spindler, *Topics in Catalysis*, **1997**, 4, 275). This process was

subsequently modified and applied to the industrial production of the imine precursor to (S)-Metolachlor, a valuable agrochemical product, then for Ciba-Giegy, now for Novartis. The production of S-Metolachlor is an example of a large-scale industrial process that depends on the homogenous hydrogenation of a prochiral imine.

Buchwald and co-workers prepared and effectively employed various chiral ansa-titanocene complexes for both hydrogenation and hydrosilylation of imines (Willoughby and Buchwald, *J. Am. Chem. Soc.*, **1992**, 114, 7562; *J. Am. Chem. Soc.*, **1994**, 116, 8952 and 11703). The need to activate the catalyst by the addition of butyl-lithium and phenyl silane limits the scope and applicability of this process. This system also suffers from the drawback of being very oxygen and water sensitive.

A recent article by Tang and Zhang provides a comprehensive review on other advances in enantioselective hydrogenation of imines (Tang and Zhang, *Chem. Rev.* 2003, 103, 3029). These include several recent examples of the development and use of chiral complexes of rhodium (Buriak et al., *Organometallics* **1996**, 15, 3161; Spindler et al., *Adv. Synth. Catal.* **2001**, 343, 68), iridium (Bianchini et al., *Organometallics* **1998**, 17, 3308; Kainz et al., *J. Am. Chem. Soc.*, **1999**, 121, 6421; Zhang et al., *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 3425) and palladium (Abe et al., *Org. Lett.* **2001**, 3, 313) and their use for the asymmetric hydrogenation of various cyclic and acyclic imines.

Despite the reported successes of some of these catalytic hydrogenation processes for imines, there are certain significant drawbacks. These include high operating pressures (typically > 50 bar H_2), high catalyst loading and the use of expensive iridium- and rhodium-based systems. In addition, activity and/or enantioselectivity tends to be either low or highly substrate dependent, which in some cases necessitates the development of an entire catalytic system and process for only one substrate or a very closely related group of substrates.

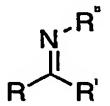
Recently Rautenstrauch et al. reported the use of metal complexes with P-N bidentate ligands (WO 02/22526 A2) and PNNP tetradentate ligands (WO 02/40155 A1)

in the catalytic hydrogenation of C=O and C=N carbon-heteroatom double bonds for the production of alcohols and amines, respectively. Noyori and coworkers have also described an efficient catalyst system generated from the complex Ru(η^6-arene)(tosyldiamine)Cl for the asymmetric hydrogenation of imines by transferring hydrogen from triethylammonium formate (Noyori et al., *Acc. Chem. Res.* **1997**, 30, 97-102).

Noyori and co-workers have pioneered the use of ruthenium complexes bearing a chelating diphosphine ligand (or two monodentate phosphines) and a chelating diamine ligand for the catalytic asymmetric hydrogenation of ketones. At least one and usually both of the chelating ligands are chiral. The various papers and patents of Noyori et al. have demonstrated the highly efficient reduction of various functionalised and unfunctionalised ketones using this class of catalysts. It was also demonstrated by Noyori and co-workers (Ohkuma et al., *J. Am. Chem. Soc.*, **1995**, 107, 2675 and 10417) that a fully isolated and characterised ruthenium(II)diphosphinediamine complex could be used as catalyst. High activity and high selectivity were generally associated with the use of chiral biaryl-phosphines (eg. Tol-BINAP and Xyl-BINAP) and diamines (eg. DPEN and DAIPEN) as ligands.

It has been reported that similar classes of Noyori-type ruthenium(II)(phosphine)$_2$(diamine) complexes could catalyse the hydrogenation and asymmetric hydrogenation of activated (aromatic) imines (Abdur-Rashid et al., *Organometallics*, **2000**, 20, 1655) or ruthenium(II)diphosphinediamine complexes (Abdur-Rashid et al., Presentations at The Canadian Society for Chemistry 83rd Conference and Exhibition, Calgary, Alberta, May 2000, and subsequently Abdur-Rashid et al., *Organometallics*, **2001**, 21, 1047). Since these publications, Chirotech Technology Limited has also reported similar imine hydrogenation processes (Cobley et al. WO 02/08169 A1; Cobley at al. *Adv. Synth. Catal.* **2003**, 345, 195) based on similar classes of complexes and imine substrates. It is noted that the reports of Abdur-Rashid

et al. and Chirotech Technology Limited both relate to the use of Noyori-type ruthenium(II)-(phosphine)$_2$(diamine) and ruthenium(II)diphosphinediamine complexes as catalysts for the reduction of *activated* imines of the Formula A shown below in which R represents an *activating* aryl group, R' represents an alkyl group and R" represents either an aryl or benzyl group.



A

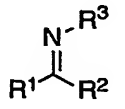
In yet another publication (Abdur-Rashid et al., PCT/CA03/00689), the use of other similar Noyori-type ruthenium(II) complexes for the hydrogenation and asymmetric hydrogenation of *unactivated* imines has been reported, in which R and R' in the Formula A simultaneously or independently represent alkyl or alkenyl substituents and R" represents either an aryl, alkyl or alkenyl substituent. The imines described in this latter publication are inherently more difficult to reduce than the activated (aromatic) analogues reported by Chirotech.

To date, there are no reports in the literature which teach the use of such Noyori-type catalysts in hydrogenation processes for the reduction of a class of imines in which, in Formula A, R represents aryl; R' represents cyclic, alkyl, alkenyl, alkynyl or aryl; and R" represents cyclic or acyclic alkyl.

There is also a continuing demand for an enantioselective imine hydrogenation procedure that allows for the facile preparation of chiral primary amines in high yields and stereoselectivities. Such chiral primary amines are desired as valuable precursors, intermediates and end products in the pharmaceutical, agrochemical, fine chemical and material industries.

SUMMARY OF THE INVENTION

It has now been found that hydrogenation of the carbon-nitrogen double bond (C=N) of imines of Formula (I) to the corresponding amines of Formula (II) can be efficiently carried out using a catalytic system including a ruthenium complex containing (1) a diamine and (2) a diphosphine or two monodentate phosphine ligands.



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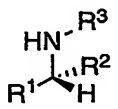
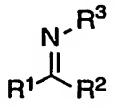


II

Therefore, the present invention includes a process for the hydrogenation of the carbon-nitrogen double bond (C=N) of imines of Formula (I) to the corresponding amines of Formula (II) comprising contacting the imines of Formula (I) with molecular hydrogen (H_2) and a catalytic system including a ruthenium complex containing (1) a diamine and (2) a diphosphine or two monodentate phosphine ligands. Such processes also relate to the asymmetric hydrogenation of prochiral imines to the chiral amines using chiral ruthenium complexes bearing chiral diphosphines or chiral monodentate phosphines and chiral diamines.

Accordingly, the present invention relates to a process for the hydrogenation and/or asymmetric hydrogenation of an imine of Formula (I) to an amine of Formula (II):



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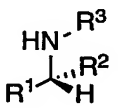


II

wherein

R^1 is selected from the group consisting of aryl and heteroaryl, which two groups are optionally substituted;

R^2 is selected from the group consisting of hydrogen, aryl, heteroaryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl and C_{3-10}heterocyclo, which latter eight groups are optionally substituted; and

R^3 is selected from the group consisting of optionally substituted C_1 to C_2 alkyl and optionally substituted C_{3-10}cycloalkyl;

or R^1 and R^2 or R^2 and R^3 are linked to form an optionally substituted ring;

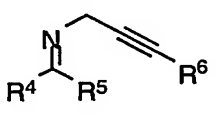
wherein the optional substituents of R^1 and R^2 are independently selected from one or more of the group consisting of halo, NO_2, OR^4, NR^4_2 and R^4, in which R^4 is independently selected from one or more of the group consisting of hydrogen, aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}cycloalkyl and C_{1-6}cycloalkenyl;

the optional substituents of R^3 are independently selected from one or more of the group consisting of halo, NO_2, OR^5, NR^5_2 and R^5, in which R^5 is independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; and

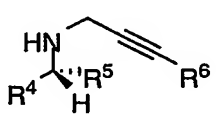
one or more of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^1, R^2 and/or R^3 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups,

said process comprising the steps of reacting imines of Formula (I) in the presence of H_2, a base and a catalytic system in which the catalytic system includes a base and a ruthenium complex comprising (1) a diamine and (2) a diphosphine ligand or monodentate phosphine ligands.

In an embodiment, the present invention also relates to a process for the hydrogenation and/or asymmetric hydrogenation of an imine of Formula (III) to an amine of Formula (IV):



III



IV

wherein

R^4 and R^5 represent simultaneously or independently any substituent, including but not limited to hydrogen, aryl, heteroaryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl and C_{3-10}heterocyclo, which latter eight groups are optionally substituted, or

R^4 and R^5 are linked together to form an optionally substituted ring;

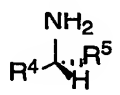
R^6 is selected from the group consisting of H, aryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl and C_{3-10}cycloalkenyl, which latter six groups are optionally substituted;

wherein the optional substituents of R^4, R^5 and R^6 are independently selected from one or more of the group consisting of halo, NO_2, OR^7, NR^7_2 and R^7, in which R^7 is independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; and

one or more of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^4, R^5 and/or R^6 are optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups,

said process comprising the steps of reacting imines of Formula (III) in the presence of H_2, a base and a catalytic system in which the catalytic system includes a base and a ruthenium complex comprising (1) a diamine and (2) a diphosphine ligand or monodentate phosphine ligands.

The present invention also relates to a very effective process for the preparation of primary amines of Formula V, by selectively removing the propargyl group from the secondary amine of the Formula IV.



V

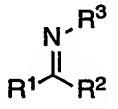
The processes of the invention may, in particular be applied to the preparation of enantiomerically enriched chiral amines of Formulae (II), (IV) and (V), or the opposite enantiomers thereof.

In embodiments of the invention, the ruthenium complex has the general Formula $RuXY(PR_3)_2(NH_2\text{-}Z\text{-}NH_2)$ (VI) or $RuXY(R_2P\text{-}Q\text{-}PR_2)(NH_2\text{-}Z\text{-}NH_2)$ (VII), where Z and Q represent a chiral or achiral linker; the ancilliary ligands PR_3 and $R_2P\text{-}Q\text{-}PR_2$ represent monodentate and bidentate phosphines, respectively; and the ligands X and Y represent an anionic ligand.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

In one of its embodiments, the present invention relates to a process for the hydrogenation and/or asymmetric hydrogenation of an imine of Formula (I) to an amine of Formula (II) and/or its other enantiomer:



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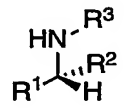


II

wherein

R^1 is selected from the group consisting of aryl and heteroaryl, which two groups are optionally substituted;

R^2 is selected from the group consisting of hydrogen, aryl, heteroaryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl and C_{3-10}heterocyclo, which latter eight groups are optionally substituted; and

R^3 is selected from the group consisting of optionally substituted C_1 to C_2 alkyl and optionally substituted C_{3-10}cycloalkyl;

or R^1 and R^2 or R^2 and R^3 are linked to form an optionally substituted ring;

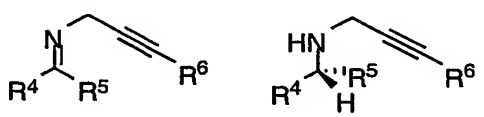
wherein the optional substituents of R^1 and R^2 are independently selected from one or more of the group consisting of halo, NO_2, OR^4, NR^4_2 and R^4, in which R^4 is independently selected from one or more of the group consisting of hydrogen, aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl;

the optional substituents of R^3 are independently selected from one or more of the group consisting of halo, NO_2, OR^5, NR^5_2 and R^5, in which R^5 is independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; and

one or more of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^1, R^2 and/or R^3 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups,

said process comprising the steps of reacting imines of Formula (I) in the presence of H_2, and a catalytic system in which the catalytic system includes a base and a ruthenium complex comprising (1) a diamine and (2) a diphosphine ligand or monodentate phosphine ligands.

In another embodiment, the present invention also relates to a process for the hydrogenation and/or asymmetric hydrogenation of an imine of Formula (III) to an amine of Formula (IV):



III IV

wherein

R^4 and R^5 represent simultaneously or independently any substituent, including but not limited to hydrogen, aryl, heteroaryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl or C_{3-10}heterocyclo, which latter eight groups are optionally substituted, or

R^4 and R^5 are linked together to form an optionally substituted ring;

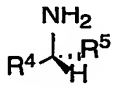
R^6 is selected from the group consisting of H, aryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl and C_{3-10}cycloalkenyl, which latter six groups are optionally substituted;

wherein the optional substituents of R^4, R^5 and R^6 are independently selected from one or more of the group consisting of halo, NO_2, OR^7, NR^7_2 and R^7, in which R^7 is independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; and

one or more of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^4, R^5 and/or R^6 are optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups,

said process comprising the steps of reacting imines of Formula (III) in the presence of H_2, and a catalytic system in which the catalytic system includes a base and a ruthenium complex comprising (1) a diamine and (2) a diphosphine ligand or monodentate phosphine ligands.

The present invention also relates to a very effective process for the preparation of primary amines of Formula V, by selectively removing the propargyl group from the secondary amine of the Formula IV.



V

The processes of the invention may, in particular be applied to the preparation of enantiomerically enriched chiral amines of Formulae (II), (IV) and (V), or the opposite enantiomers thereof. Suitably, the processes of the present invention provide an effective means of preparing a wide range of chiral amines. It is desirable that the enantiomeric enrichment of the amines (II) and (IV) is at least 50% ee, and more suitably at least 80% ee, or higher. If necessary, any shortfall in ee can be subsequently corrected by crystallization techniques known by persons skilled in the art. It is also desirable to achieve a high conversion of substrate to product, suitably at least 80% conversion, and more suitably at least 90% conversion.

The term "aryl" as used herein means an unsaturated aromatic carbocyclic group containing from six to fourteen carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). In an embodiment of the invention, aryl includes phenyl and naphthyl, in particular phenyl.

The term "heteroaryl" as used herein means an unsaturated aromatic carbocyclic group containing from five to fourteen carbon atoms having a single ring or multiple condensed (fused) and wherein one or more, suitably one or three, more suitably one to two, even more suitably one of the carbon atoms in the aromatic group is replaced with a heteroatom selected from the group consisting of O, S, and N which, where possible, is optionally substituted with one or more alkyl groups. Examples of suitable heteroaryl groups include, but are not limited to, pyridyl, thienyl, furanyl, pyrrolyl, and their corresponding benzo-fused ring systems (for example indolyl and benzofuranyl) and the like.

The term "alkyl" as used herein means a saturated, linear or branched alkyl group containing the specified number of carbon atoms.

The term "cycloalkyl" as used herein means a saturated carbocyclic group containing the specified number of carbon atoms and having a single ring (e.g.,

cyclohexyl and cyclopentyl) or multiple condensed (fused) rings (e.g decahydronaphthalene and adamantanyl).

The term "alkenyl" as used herein means an unsaturated, linear or branched alkenyl group containing the specified number of carbon atoms and includes vinyl, allyl, butenyl and the like. The alkenyl groups may contain any number of double bonds. Suitably, the alkenyl group contains one double bond.

The term "cycloalkenyl" as used herein means a unsaturated carbocyclic group containing the specified number of carbon atoms and having a single ring (e.g., cyclohexenyl and cyclopentenyl) or multiple condensed (fused) rings (e.g octahydronaphthalene). The cycloalkenyl groups may contain any number of double bonds. Suitably, the cycloalkenyl group contains one double bond

The term "alkynyl" as used herein means an unsaturated, linear or branched alkynyl group containing the specified number of carbon atoms and includes ethynyl, propynyl, propargyl, butynyl and the like. The alkynyl groups may contain any number of triple bonds. Suitably, the alkynyl group contains one triple bond.

The term "halo" as used herein means halogen and includes chloro, bromo, iodo, fluoro and the like.

When R^1 and R^2 are linked together, or with R^3, or when R^5 and R^6 are linked together to form one or more carbocyclic rings, said rings may contain from three to twelve atoms, suitably three to ten atoms, having a single ring structure or multiple condensed (fused) ring structure. Further in the rings, one or more, suitably one or two, more suitably one, of the carbon atoms may be substituted with a heteroatom selected from O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups. Suitably, one or more, more suitably one or two, even more suitably one, of the carbon atoms of the ring may be substituted with a heteroatom selected from O, S, N, NH and N-CH_3.

In the compounds of Formula I, R^1 is selected from the group consisting of aryl and heteroaryl, which two groups are optionally substituted. In embodiments of the invention R^1 is optionally substituted aryl, suitably optionally substituted phenyl, more suitably unsubstituted phenyl.

Further, in the compounds of Formula I, R^2 is selected from the group consisting of hydrogen, aryl, heteroaryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl and C_{3-10}heterocyclo, which latter eight groups are optionally substituted. In embodiments of the invention R^2 is selected from the group consisting of hydrogen, aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl, which latter six groups are optionally substituted. In further embodiments of the invention, R^2 is selected from the group consisting of hydrogen, aryl and C_{1-6}alkyl, which latter two groups are optionally substituted. In still further embodiments of the invention R^2 is selected from the group consisting of hydrogen, phenyl, and C_{1-6}alkyl, which latter two groups are optionally substituted. In still further embodiments of the invention R^2 is selected from the group consisting of hydrogen, unsubstituted phenyl and methyl.

Still further, in the compounds of Formula I, R^3 is selected from the group consisting of optionally substituted C_1 to C_2 alkyl and optionally substituted C_{3-10}cycloalkyl. In embodiments of the invention, R^3 is selected from the group consisting of optionally substituted C_1 to C_2 alkyl and optionally substituted C_{3-6}cycloalkyl. In a further embodiment of the invention, R^3 is methyl, ethyl i-propyl (ethyl substituted with methyl), cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, which latter four groups are unsubstituted.

The invention also extends to compounds of Formula I wherein R^1 and R^2 or R^2 and R^3 are linked to form an optionally substituted ring. In embodiments of the invention R^2 and R^3 (including the atoms to which they are attached) are linked to form an optionally substituted, suitably unsubstituted, 5- or 6-membered ring, with the linking group being a C_3 to C_4 alkylene group.

As stated above, the optional substituents for R^1 and R^2 in the compounds of Formula I, are independently selected from one or more of the group consisting of halo, NO_2, OR^4, NR^4_2 and R^4, in which R^4 is independently selected from one or more of the group consisting of hydrogen, aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl, and the optional substituents of R^3 are independently selected from one or more of the group consisting of halo, NO_2, OR^5, NR^5_2 and R^5, in which R^5 is independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl. In embodiments of the invention, the optional substituents for R^1 and R^2 in the compounds of Formula I, are independently selected from one or more of the group consisting of halo, NO_2, OR^4, NR^4_2 and R^4, in which R^4 is independently selected from one or more of the group consisting of hydrogen, aryl and C_{1-4}alkyl, and the optional substituents of R^3 are independently selected from one or more of the group consisting of halo, NO_2, OR^5, NR^5_2 and R^5, in which R^5 is independently selected from the group consisting of C_{1-4}alkyl. In further embodiments of the invention, the optional substituents for R^1 and R^2 in the compounds of Formula I, are independently selected from one or more of the group consisting of halo, NO_2, OH, OCH_3, NH_2, $N(CH_3)_2$, CH_3 and phenyl, and the optional substituents of R^3 are independently selected from one or more of the group consisting of halo, NO_2, OH, OCH_3, NH_2, $N(CH_3)_2$ and CH_3.

The compounds of Formula I also include those in which one or more of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^1, R^2 and/or R^3 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups. In an embodiment of the invention, one to three, suitably one or two, more suitably one, of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^1, R^2 and/or R^3 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, NH and N-CH_3.

In the compounds of Formula III, R^4 and R^5 represent simultaneously or independently any substituent, including but not limited to hydrogen, aryl, heteroaryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl or C_{3-10}heterocyclo, which latter eight groups are optionally substituted. In embodiments of the invention, R^4 and R^5 represent simultaneously or independently hydrogen, aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkenyl, which latter six groups are optionally substituted. In further embodiments of the invention, R^4 and R^5 represent simultaneously or independently hydrogen, aryl or C_{1-6}alkyl, which latter two groups are optionally substituted. In still further embodiments of the invention R^4 and R^5 represent simultaneously or independently hydrogen, phenyl, and C_{1-6}alkyl, which latter two groups are optionally substituted. In still further embodiments of the invention R^4 and R^5 represent simultaneously or independently hydrogen, unsubstituted phenyl or methyl.

Further, in compounds of Formula III, R^4 and R^5 may be linked together to form an optionally substituted ring. In embodiments of the invention R^4 and R^5 (including the atoms to which they are attached) are linked to form an optionally substituted, suitably unsubstituted, 5- or 6-membered ring, with the linking group being a C_3 to C_4 alkylene group.

The present invention also involves the use of compounds of Formula III in which R^6 is selected from the group consisting of H, aryl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl and C_{3-10}cycloalkenyl, which latter six groups are optionally substituted. In embodiments of the invention, R^6 is selected from the group consisting of H, aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl, which latter six groups are optionally substituted. In still further embodiments of the invention, R^6 is selected from the group consisting of H and C_{1-4}alkyl, suitably H.

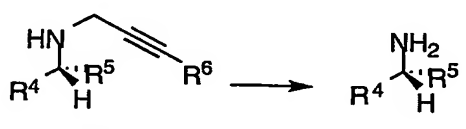
As stated above, the optional substituents for R^4, R^5 and R^6 in the compounds of Formula III, are independently selected from one or more of the group consisting of

halo, NO_2, OR^7, NR^7_2 and R^7, in which R^7 is independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl. In embodiments of the invention, the optional substituents for R^4, R^5 and R^6 in the compounds of Formula III, are independently selected from one or more of the group consisting of halo, NO_2, OR^7, NR^7_2 and R^7, in which R^7 is independently selected from one or more of the group consisting of C_{1-4}alkyl. In further embodiments of the invention, the optional substituents for R^4, R^5 and R^6 in the compounds of Formula III, are independently selected from one or more of the group consisting of halo, NO_2, OH, OCH_3, NH_2, $N(CH_3)_2$ and CH_3,

The compounds of Formula III also include those in which one or more of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^4, R^5 and/or R^6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more C_{1-6}alkyl groups. In an embodiment of the invention, one to three, suitably one or two, more suitably one, of the carbon atoms in the alkyl, alkenyl and/or alkynyl groups of R^4, R^5 and/or R^6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, NH and N-CH_3.

As to any of the above groups in the compounds of Formulae I-IV, that contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

The present invention also relates to a very effective process for the preparation of primary amines of Formula V, wherein $R^4$and R^5 are as defined in Formula IV, by selectively removing the propargyl group from the secondary amine of the Formula IV.



IV V

The propargyl group can be removed using any suitable method, for example using $TiCl_3$ and lithium according to the procedure of Banerji et al. (*Tetrahedron Lett.* 1999, 40, 767-770).

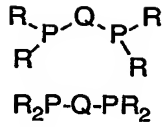
The process of the invention involves the catalytic hydrogenation or asymmetric hydrogenation of an imine of the Formula I or III, in the presence of a base and an achiral or chiral ruthenium complex containing a diamine ligand of the general Formula $RuXY(PR_3)_2(NH_2\text{-}Z\text{-}NH_2)$ (VI) or $RuXY(R_2P\text{-}Q\text{-}PR_2)(NH_2\text{-}Z\text{-}NH_2)$ (VII), where Z and Q represent a chiral or achiral linker; the ancilliary ligands PR_3 and $R_2P\text{-}Q\text{-}PR_2$ represent monodentate and bidentate phosphines, respectively; and the ligands X and Y represent an anionic ligand. More particularly, the ligands X and Y are selected from the group consisting of Cl, Br, I, H, hydroxy, alkoxy and acyloxy.

In embodiments of the invention, the ligand PR_3:

PR_3

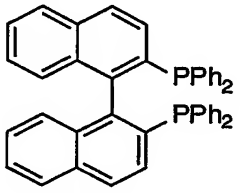
represents a chiral or achiral monodentate phosphine ligand in which R is simultaneously or independently selected from the group consisting of optionally substituted linear and branched alkyl containing 1 to 8 carbon atoms, optionally substituted linear and branched alkenyl containing 2 to 8 carbon atoms, optionally substituted cycloalkyl, optionally substituted aryl, OR and NR_2; or two R groups bonded to the same P atom are bonded together to form a ring having 5 to 8 atoms and including the phosphorous atom to which said R groups are bonded.

In embodiments of the present invention, the ligand $R_2P\text{-}Q\text{-}PR_2$:

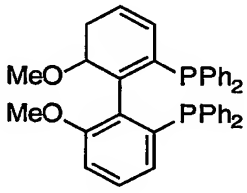


represents a bidentate ligand in which R is simultaneously or independently selected from the group consisting of optionally substituted linear and branched alkyl containing 1 to 8 carbon atoms, optionally substituted linear and branched alkenyl containing 2 to 8 carbon atoms, optionally substituted cycloalkyl, optionally substituted aryl, OR and NR_2; or two R groups bonded to the same P atom are bonded together to form a ring having 5 to 8 atoms and including the phosphorous atom to which said R groups are bonded; and Q is selected from the group consisting of linear and cyclic C_2-C_7 alkylene, optionally substituted metallocenediyl and optionally substituted C_6-C_{22} arylene.

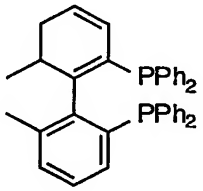
In further embodiments of the invention, the ligand R_2P-Q-PR_2 is chiral and includes atropisomeric bis-tertiary phosphines, in which the two phosphorus atoms are linked by a biaryl backbone. More particularly, the ligand R_2P-Q-PR_2 is selected from the group consisting of BINAP, BIPHEP and BIPHEMP:



BINAP

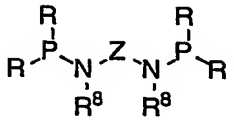


BIPHEP



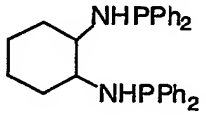
BIPHEMP

In embodiments of the invention, the bidentate phosphine is a chiral or achiral ligand of the type R_2P-NR^5-Z-NR^5-PR_2:

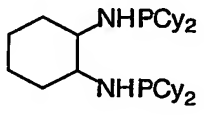


$R_2P\text{-}NR^8\text{-}Z\text{-}NR^8\text{-}PR_2$

wherein each R, taken separately, is independently selected from the group consisting of optionally substituted linear and branched alkyl group containing 1 to 8 carbon atoms, optionally substituted linear and branched alkenyl group containing 2 to 8 carbon atoms, optionally substituted cycloalkyl, optionally substituted aryl, OR and NR_2; or two R groups bonded to the same P atom are bonded together to form a ring having 5 to 8 atoms and including the phosphorous atom to which said R groups are bonded; each R^8, is independently selected from the group consisting of hydrogen, optionally substituted linear and branched alkyl group containing 1 to 8 carbon atoms, optionally substituted linear and branched alkenyl group containing 2 to 8 carbon atoms, optionally substituted cycloalkyl, optionally substituted aryl, OR and NR_2; and Z is optionally substituted linear and cyclic C_2-C_7 alkylene, optionally substituted metallocenediyl and optionally substituted C_6-C_{22} arylene. More particularly, the ligand $R_2P\text{-}NR^5\text{-}Z\text{-}NR^5\text{-}PR_2$ (V) is selected from the group consisting of DPPACH and DCYPPACH:

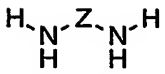


DPPACH



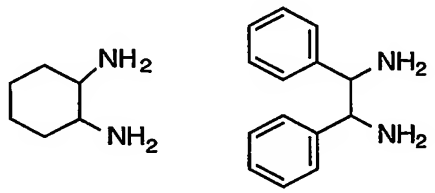
DCYPPACH

The present invention also includes within its scope the process in which the diamine ligand has the Formula $NH_2\text{-}Z\text{-}NH_2$:



NH_2-Z-NH_2

wherein Z is selected from the group consisting of optionally substituted linear and cyclic C_2-C_7 alkylene, optionally substituted metallocenediyl and optionally substituted C_6-C_{22} arylene. In further embodiments of the invention, the diamine ligand is chiral and includes (1) compounds in which at least one of the amine-bearing centers is stereogenic, (2) compounds in which both of the amine-bearing centers are stereogenic and (3) atropisomeric bis-tertiary diamines, in which the two nitrogen atoms are linked by a biaryl backbone. Still further, the diamine ligand NH_2-Z-NH_2 is selected from the group consisting of CYDN and DPEN:

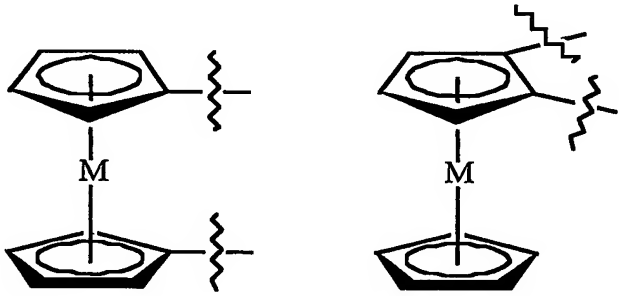


CYDN DPEN

In embodiments of the invention, the diamine is a bidentate ligand of the Formula D-Z-NHR^9 in which Z is selected from the group consisting of optionally substituted linear and cyclic C_2-C_7 alkylene, optionally substituted metallocenediyl and optionally substituted C_6-C_{22} arylene; D is an amido group donor or a chalcogenide radical selected from the group consisting of O, S, Se and Te; NHR^9 is an amino group donor in which R^9 is selected from the group consisting of hydrogen, optionally substituted linear and branched alkyl group containing 1 to 8 carbon atoms, optionally substituted linear and branched alkenyl group containing 2 to 8 carbon atoms, optionally substituted cycloalkyl and optionally substituted aryl. In more particular embodiments of the

invention, D is NR^{10}, in which R^{10} is selected from the group consisting of $S(O)_2R^{11}$, $P(O)(R^{11})_2$, $C(O)R^{11}$, $C(O)N(R^{11})_2$ and $C(S)N(R^{11})_2$, in which R^{11} is independently selected from the group consisting of hydrogen, optionally substituted linear and branched alkyl group containing 1 to 8 carbon atoms, optionally substituted linear and branched alkenyl group containing 2 to 8 carbon atoms, optionally substituted cycloalkyl and optionally substituted aryl. In embodiments of the invention, the diamine is chiral and includes (1) compounds in which the amine-bearing center is stereogenic, (2) compounds in which both the donor-bearing (D) and amine-bearing centers are stereogenic. More particularly, the diamine is $CH_3C_6H_4SO_3NCHPhCHPhNH_2$.

The term "metallocenediyl" as used herein refers to a bivalent metallocene group, typically having one of the following structures:



in which M is a metal, for example iron (Fe).

The term "arylene" as used herein includes biaryldiyl groups and refers to a bivalent group comprising one to three, suitably one to two, aryl groups linked together. Examples of arylene groups include, but are not limited to biphenyldiyl and binaphthyldiyl.

The term "optionally substituted" as used herein in the various ligands for the ruthenium complexes means that the corresponding group is either unsubstituted or substituted. When a group is substituted the substituents may include one to five, sutiably one to three, more suitably one to two, groups selected from but not limited to

alkyl, alkoxy, polyalkyleneglycol, carboxylic esters, OH, halo, cycloalkyl, aryl, and halo-substituted-aryl. As to any of the above groups that contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

The term "halo" as used herein means halogen and includes chloro, fluoro, bromo and iodo.

The term "alkoxy" as used herein means saturated, cyclic, linear or branched O-alkyl groups containing from one to ten, suitably one to eight, more suitably one to six carbon atoms and includes methoxy, ethoxy, propoxy, t-butoxy and the like.

The term "acyloxy" as used herein means saturated, cyclic, linear or branched O-acyl groups containing from one to ten, suitably one to eight, more suitably one to six carbon atoms and includes acetoxy and the like.

The ruthenium catalyst complexes may be prepared, for example, as described by Abdur-Rashid et al. (*Organometallics*, 2001, 21, 1047). Many of the ligands described above are known in the art and, unless specified otherwise in the Examples, are obtained according to methods known in the art. The ligands that are new can be obtained by modifying known procedures according to the knowledge of a person skilled in the art.

As previously mentioned, the catalytic system characterizing the process of the present invention comprises a base. Said base can be the substrate itself, if the latter is basic, or any conventional base. One can cite, as non-limiting examples, organic non-coordinating bases such as DBU, tertiary organic amines, phosphazene bases, an alkaline or alkaline-earth metal carbonate, a carboxylate salt such as sodium or potassium acetate, or an alcoholate or hydroxide salt. Suitable bases are the alcoholate or hydroxide salts selected from the group consisting of the compounds of Formula $(R^{12}O)_2M'$ and $R^{12}OM''$, wherein M' is an alkaline-earth metal, M'' is an alkaline metal and R^{12} stands

for hydrogen or a C_1 to C_6 linear or branched alkyl radical. Also within the scope of the present invention, the base may be an organic non-coordinating base.

A typical process implies the mixture of the substrate with the ruthenium complex and a base, possibly in the presence of a solvent, and then treating such a mixture with molecular hydrogen at a chosen pressure and temperature.

The complexes can be added to the reaction medium in a large range of concentrations. As non-limiting examples, one can cite substrate to complex (S/com) ratio of 20 to 10^5. Preferably, the substrate to complex ratio will be in the range of 1000 to 10^4, respectively. It goes without saying that the optimum concentration of complex will depend on the nature of the latter and on the pressure of H_2 used during the process.

Useful quantities of base, added to the reaction mixture, may be comprised in a relatively large range. One can cite, as non-limiting examples, ranges between 1 to 50000 molar equivalents relative to the complex, preferably 10 to 2000. However, it should be noted that it is also possible to add a small amount of base (e.g. base/com = 1 to 3) to achieve high hydrogenation yields.

The hydrogenation reaction can be carried out in the presence or absence of a solvent. When a solvent is required or used for practical reasons, then any solvent current in hydrogenation reactions can be used for the purposes of the invention. Non-limiting examples include aromatic solvents such as benzene, toluene or xylene, hydrocarbon solvents such as hexane or cyclohexane, ethers such as tetrahydrofuran, or yet primary or secondary alcohols, or mixtures thereof. Still further, the solvent may be an amine solvent. A person skilled in the art is well able to select the solvent most convenient in each case to optimize the hydrogenation reaction.

In the hydrogenation process of the invention, the reaction can be carried out at a H_2 pressure comprised between 10^5 Pa and $80x10^5$ Pa (1 to 80 bars). Again, a person skilled in the art is well able to adjust the pressure as a function of the catalyst load and

of the dilution of the substrate in the solvent. As examples, one can cite typical pressures of 1 to $40x10^5$ Pa (1 to 40 bar).

The temperature at which the hydrogenation can be carried out is comprised between 0°C and 100°C, more preferably in the range of between 20°C and 60°C. Of course, a person skilled in the art is also able to select the preferred temperature as a function of the melting and boiling point of the starting and final products.

The following non-limiting examples are illustrative of the present invention:

EXAMPLES

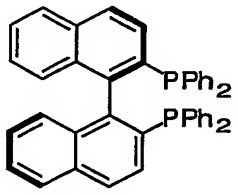
Materials and Methods

The invention will now be described in further details by way of the following examples, wherein the temperatures are indicated in degrees centigrade and the abbreviations have the usual meaning in the art. The ligand R,R-DPPACH is a known compound that was previously used in rhodium complexes for the hydrogenation of C=C double bonds (Fioriani et al., *J. Mol. Catal.*, **1979**, 5, 303), (Onuma et al., *Bull. Chem. Soc. Jpn.*, **1980**, 53, 2012; *Chem. Lett.*, **1980**, 5, 481).

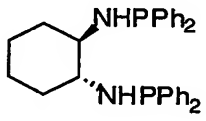
All the procedures described hereafter have been carried out under an inert atmosphere unless stated otherwise. Hydrogenations were carried out in open glass tubes placed inside a stainless steel autoclave or Schlenk flasks attached to a vacuum line. Hydrogen gas was used as received. All preparations and manipulations were carried out under H_2, N_2 or Ar atmospheres with the use of standard Schlenk, vacuum line and glove box techniques in dry, oxygen-free solvents. Tetrahydrofuran (THF), diethyl ether (Et_2O) and hexanes were dried and distilled from sodium benzophenone ketyl. Deuterated solvents were degassed and dried over activated molecular sieves. Ruthenium trichloride, triphenylphosphine, R,R-DPEN, R,R-CYDN, ketones and amines were purchased from Aldrich. Imines were prepared using previously reported procedures (*Organometallics* **2001**, 21, 1047; *J. Am. Chem. Soc* **1996**, 118, 6784; *J. Am. Chem. Soc* **1994**, 116, 8952; *J. Org. Chem. Soc* **1993**, 58, 7627). Selective removal of

the N-propargyl protecting group from amines followed the procedure which was previously reported by Banerji et al. (*Tetrahedron Lett.* **1999**, 40, 767). The precursor complex $RuHCl(PPh_3)_3$ was prepared by a modification of the procedure reported by Schunn et al. (*Inorg. Synth.* **1970**, 131). The complexes RuHCl(R-BINAP)(PPh_3), RuHCl(R,R-DPPACH)(PPh_3), RuHCl(R-BINAP)(R,R-CYDN), RuHCl(R-BINAP)(R,R-DPEN), RuHCl(R,R-DPPACH)(R,R-CYDN) and RuHCl(R,R-DPPACH)(R,R-DPEN) were prepared as described in *Organometallics*, 2001, 21, 1047. NMR spectra were recorded on either a Varian Gemini 300 MHz spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C and 121.5 for ^{31}P) or a Varian Unity 400 MHz spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). All ^{31}P spectra were recorded with proton decoupling and ^{31}P chemical shifts were measured relative to 85% H_3PO_4 as an external reference. ^1H and ^{13}C chemical shifts were measured relative to partially deuterated solvent peaks but are reported relative to tetramethylsilane.

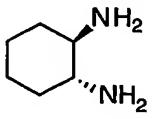
Structure of the ligands used in the examples are shown below:



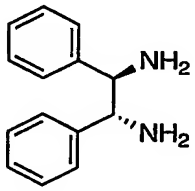
R-BINAP



R,R-DPPACH



R,R-CYDN



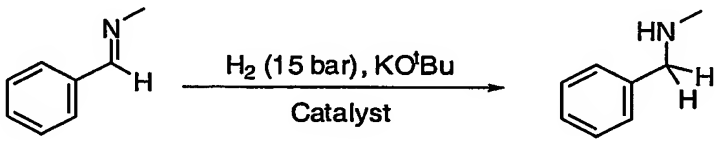
R,R-DPEN

Example 1: General Procedure for Catalytic hydrogenation

A solution of the required imine dissolved in benzene was added to a mixture of the catalyst (0.1 – 0.5%) and KO^{t}Bu (10-50 mg) in a 50 ml Parr hydrogenation reactor (fitted with a removable glass liner and a magnetic stirring bar). The reactor was then purged several times with H_2 gas, pressurized to the desired pressure (10-50 bar) and stirred vigorously at the required temperature. The pressure was periodically released and the hydrogenation reaction monitored by removing a sample of the reaction mixture and measuring its ^{1}H NMR spectrum. If required, the mixture was re-pressurized with H_2 gas and the reaction continued until either the hydrogenation is complete or no further change in the composition was observed (NMR). Upon completion, hexane (10 ml) was added to the reaction mixture, which was then eluted (hexane) through a short column of silica gel in order to remove the spent catalyst and KO^{t}Bu. Evaporation of the hexane under reduced pressure yielded the product.

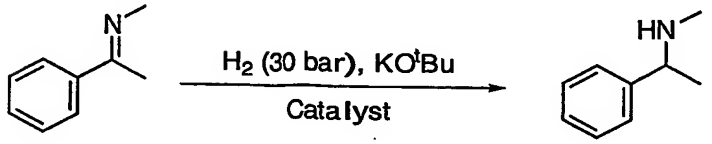
Results of the Catalytic hydrogenation using the series of RuHCl(diphosphine)(diamine) complexes are summarized below.

Example 1.1: Hydrogenation of N-(Benzylidene)methylamine



Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	1000	100	24
RuHCl(R-BINAP)(R,R-DPEN)	1000	100	24
RuHCl(R,R-DPPACH)(R,R-CYDN)	1000	100	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	1000	100	24

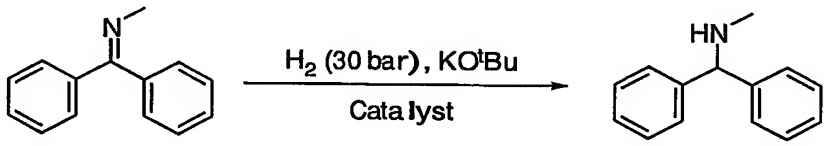
Example 1.2: Hydrogenation of N-(1-Phenylethylidene)methylamine



Catalyst	S:C	Conv. (%)	Time/hr	ee(%)*
RuHCl(R-BINAP)(R,R-CYDN)	600	98	24	62 (S)
RuHCl(R-BINAP)(R,R-DPEN)	600	97	24	71 (S)
RuHCl(R,R-DPPACH)(R,R-CYDN)	600	100	24	48 (S)
RuHCl(R,R-DPPACH)(R,R-DPEN)	600	100	24	51 (S)

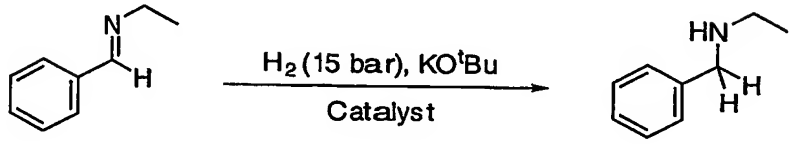
* The ee was determined from the rotation (α_D) of N-methyl-1-phenylethylamine.

Example 1.3: Hydrogenation of N-(Benzylhydrylidene)methylamine



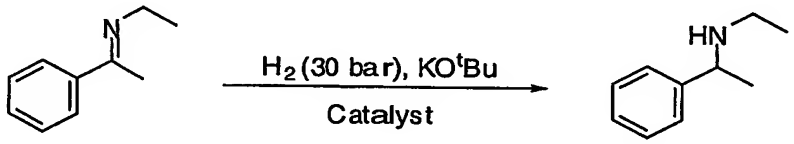
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	500	100	24
RuHCl(R-BINAP)(R,R-DPEN)	500	100	24
RuHCl(R,R-DPPACH)(R,R-CYDN)	500	100	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	500	100	24

Example 1.4: Hydrogenation of N-(Benzylidene)ethylamine



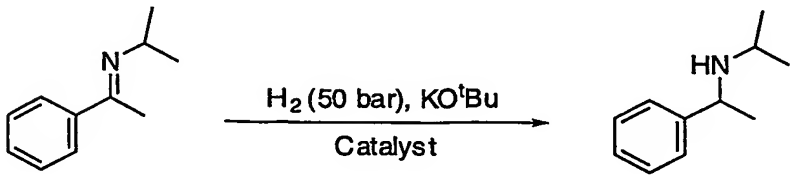
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	1000	100	24
RuHCl(R-BINAP)(R,R-DPEN)	1000	100	24
RuHCl(R,R-DPPACH)(R,R-CYDN)	1000	100	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	1000	100	24

Example 1.5: Hydrogenation of N-(1-Phenylethylidene)ethylamine



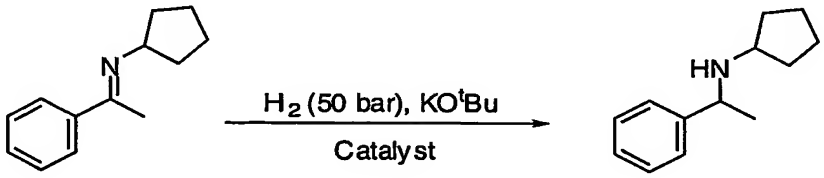
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	500	95	36
RuHCl(R-BINAP)(R,R-DPEN)	500	98	36
RuHCl(R,R-DPPACH)(R,R-CYDN)	500	100	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	500	100	24

Example 1.6: Hydrogenation of N-(1-Phenylethylidene)-2-propylamine



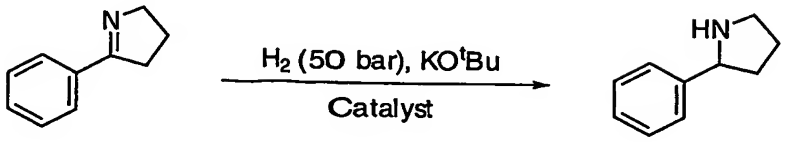
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	500	75	36
RuHCl(R-BINAP)(R,R-DPEN)	500	72	36
RuHCl(R,R-DPPACH)(R,R-CYDN)	500	87	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	500	91	24

Example 1.7: Hydrogenation of N-(1-Phenylethylidene)cyclopentylamine



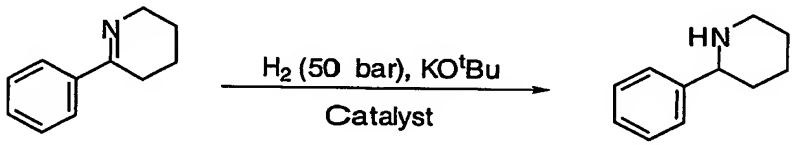
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	200	91	36
RuHCl(R-BINAP)(R,R-DPEN)	200	83	36
RuHCl(R,R-DPPACH)(R,R-CYDN)	200	97	36
RuHCl(R,R-DPPACH)(R,R-DPEN)	200	95	36

Example 1.8: Hydrogenation of 2-phenyl-1-pyrroline



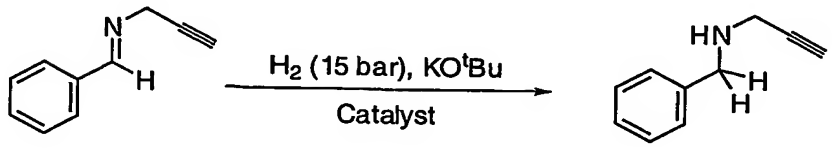
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	200	92	36
RuHCl(R-BINAP)(R,R-DPEN)	200	89	36
RuHCl(R,R-DPPACH)(R,R-CYDN)	200	97	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	200	93	24

Example 1.9: Hydrogenation of 2-phenyl-3,4,5,6-tetrahydropyridine



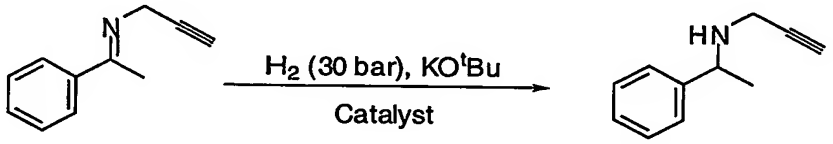
Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	200	82	36
RuHCl(R-BINAP)(R,R-DPEN)	200	76	36
RuHCl(R,R-DPPACH)(R,R-CYDN)	200	94	36
RuHCl(R,R-DPPACH)(R,R-DPEN)	200	88	36

Example 1.10: Hydrogenation of N-(Benzylidene)propargylamine



Catalyst	S:C	Conv. (%)	Time/hr
RuHCl(R-BINAP)(R,R-CYDN)	1000	100	24
RuHCl(R-BINAP)(R,R-DPEN)	1000	100	24
RuHCl(R,R-DPPACH)(R,R-CYDN)	1000	100	24
RuHCl(R,R-DPPACH)(R,R-DPEN)	1000	100	24

Example 1.11: Hydrogenation of N-(1-Phenylethylidene)propargylamine

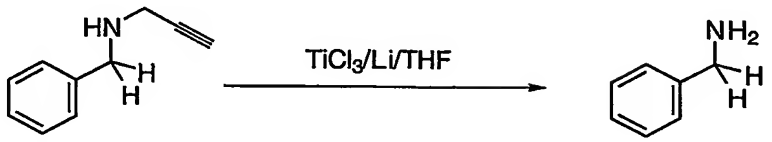


Catalyst	S:C	Conv. (%)	Time/hr	ee*
RuHCl(R-BINAP)(R,R-CYDN)	1000	97	24	78 (S)
RuHCl(R-BINAP)(R,R-DPEN)	1000	100	24	67 (S)
RuHCl(R,R-DPPACH)(R,R-CYDN)	1000	100	24	52 (S)
RuHCl(R,R-DPPACH)(R,R-DPEN)	1000	100	24	51 (S)

* The ee was determined from the rotation (α_D) of the de-protected 1-phenylethylamine.

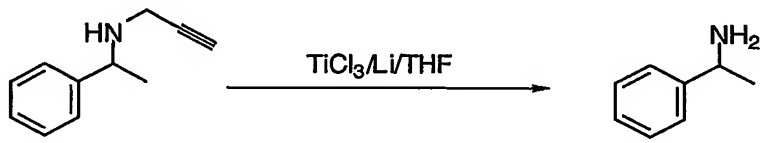
Example 2: Removal of the Protecting Group

Example 2.1: Removal of the protecting group from N-(Benzyl)propargylamine in Example 1.10



The procedure reported by Banerji et al. (*Tetrahedron Lett.* 1999, 40, 767-770) was used to selectively remove the N-propargyl protecting group. A mixture of $TiCl_3$ (1.54 g, 10 mmol) and lithium (231 mg, 33 mmol) was refluxed for 3 hours under argon in THF (40 ml). A solution of N-(Benzyl)propargylamine (500 mg, 3.4 mmol) in THF (5 ml) was added to the LVT reagent and stirred for 1 hour at room temperature. The reaction mixture was diluted with hexane-ethyl acetate mixture (70:30) and filtered through celite. The filtrate washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified using chromatography (SiO_2) to yield benzylamine (245 mg, 66 %).

Example 2.2: Removal of protecting group from N-(1-Phenylethyl)propargylamine in Example 1.11



A solution of N-(1-Phenylethyl)propargylamine (500 mg, 3.1 mmol) in THF (5 ml) was added to the LVT reagent prepared as described in Example 2.1 above, and the resulting mixture stirred for 2 hours at room temperature. The reaction mixture was diluted with hexane-ethyl acetate mixture (70:30) and filtered through celite. The filtrate washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified

using chromatography (SiO_2) to yield 1-phenylethylamine (290 mg, 77 %). The rotation (α_D) of the de-protected 1-phenylethylamine was used to determine the ee of the products in Example 1.11.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.